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PERIARTERITIS NODOSA

Clinical interest in periarteritis nodosa has advanced apace with a growing appreciation of its pathologic and clinical implications. Its etiologic background is shrouded in a confusion of theories. While occasional workers have reported streptococcemia in these patients, the majority of such studies have been negative. With certain possible exceptions (von Haun, 1920, by the injection of the blood; Harris and Friedrichs, 1922, by the injection of the Berkefeld filtrate of an emulsion of a periarteritic nodule), the experimental reproduction of the disease has been unsuccessful. While suspicion has from time to time been directed toward a causal relation of typhus fever, syphilis and other diseases to periarteritis nodosa, two possible etiologic factors seem to hold the ascendancy in recent thought. In the first place the frequence of a rheumatic history in patients with periarteritis nodosa and the common concurrence of the histologic lesions of the two diseases have given strong support to the assumption of a relationship between them. If such a circumstance be granted more than coincidental importance, this relation might be causal or it might depend upon the existence of a common basis for the two diseases. Secondly, the factor of hyperergy (Grüber, 1925, 1926) receives substantial support in the recent experimental work of Masugi and Sato (1934).

The pathologic sequence suggests the entrance of the inflammatory agent by the perivascular lymphatics to the adventitia of the smaller arteries and arterioles (Klotz, 1917). Arkin (1930) divides the pathologic changes of periarteritis nodosa into four stages:

1. Alterative-degenerative
2. Acute inflammatory
3. Granulation tissue
4. Healed end-stage.

While this formulation is useful, it is admittedly too broad for general application. The disease is characterized by necrosis of the media, fibrinous exudate and cellular infiltration with lymphocytes, plasma cells and eosinophils that may involve all layers of the affected vessel. Intimal proliferation favors the occurrence of thrombosis and these thrombi tend to become canalized. Degeneration of the muscle fibers of the media coupled with the rupture of the elastic lamina determines the development of multiple small aneurysms. Repair is initiated by a fibroblastic proliferation coextensive with the antecedent morbid change. In turn through encroachment upon the nutrition to vital organs, a new train of pathologic and clinical manifestations may arise from degeneration, infarction, gangrene, atrophy and scarring in the parts supplied. The distribution of these pathologic changes follows no known rule. In Grüber's analysis of 108 cases of periarteritis nodosa (1926) the kidneys were affected in 80; the heart in 71; the liver in 66; the gastro-intestinal tract in 50; muscles in 32; the pancreas in 36; peripheral nerves in 20; the spleen and adrenal bodies each in 15; the gall bladder in 13; subcutaneous tissue in 14; and other organs, less than 10 each. The routine technique of necropsies itself varies widely and this circumstance may explain the relatively low incidence of the characteristic periarteritic lesions in the peripheral nerves and voluntary muscles in this series gathered from many sources.

The pathologic changes of periarteritis nodosa and their irregular distribution bespeak a varied, inconstant clinical picture. A peculiar disparity between the extent of the anatomic lesions and the functional disturbances in its subject has been remarked (Carr, 1930). Attempts to regiment its several manifestations into fixed stages have been singularly unfruitful. The clinical tetrad evolved by Meyer (1921) and Brinkmann (1922) affords a most useful direction of diagnostic approach. This includes, (1) chlorotic marasmus, (2) polyneuritis and polymyositis, (3) gastro-intestinal disturbances, such as a sense of pressure, vomiting, bloody diarrhoea, perforation and peritonitis, and (4) nephritis. It is predominantly a disease of the male sex, but there appears to be no age factor of predilection, instances having been reported from three months to seventy-one years. As a rule pain and tenderness in the extremities initiate the clinical picture. This pain is not confined to nerve trunks but involves the muscles as well. It may be continuous and dull or at times it may become intractable to the ordinary analgesics. The appearance of the subcutaneous periarteritic nodules is delayed and from a diagnostic standpoint, disappointingly inconstant. Fever constitutes an important feature in about 40 per cent of the cases (Curtis and Coffey, 1934). When it occurs, it is apt to run an irregularly remittent course. Pallor and weakness advance steadily. Wasting is marked. In certain instances visceral involvement may supervene to augment this picture of peripheral vascular invasion, while in others the picture may be entirely visceral from the outset.

Many clinical subdivisions have been suggested upon the basis of these visceral manifestations of periarteritis nodosa, but such efforts become highly artificial. Abdominal cramps with nausea, vomiting and diarrhoea may lead to a suspicion of an acute inflammatory condition requiring surgery. Melena, intestinal perforation and peritonitis may cloud the issue. The peculiar predilection of the affection for

SCIENTIFIC SESSIONS

The Fourteenth Scientific Sessions of the American Heart Association will be held in the Empire Room, Sir Francis Drake Hotel, San Francisco, California, June 10 and 11, 1938. The general cardiac program will be given on Friday, June 10, and the program of the Section for the Study of the Peripheral Circulation on Saturday, June 11.

the wall of the gall bladder evokes a further group of symptoms and increases the danger of diagnostic confusion. Jaundice is commonly encountered. Pancreatic involvement may induce faults in sugar metabolism as well as localizing symptoms. The early phase of renal invasion may suggest an acute nephritis but renal insufficiency may eventually result from the encroachment upon its nutrition as in arteriolosclerosis of the kidney. Cerebral symptoms occasionally attend the acute phase. Psychic disturbances are met and the picture may be that of an encephalitis or an encephalo-myelitis (Urechia and Elekes, 1934). Vascular accidents in the central nervous system and elsewhere may be anticipated either from the rupture of an aneurysm or from thrombosis. Bronchial asthma has occurred occasionally on the background of periarteritis nodosa (Strong, 1928). Angina pectoris and actual coronary occlusion are infrequent sequels of coronary involvement in this condition. Arrhythmias of varying orders may precede myocardial incompetence with its attendant symptoms. Arterial hypertension usually bespeaks renal involvement but it may occur independently of this change in periarteritis nodosa. Lastly endocrine disturbances may in rare instances develop upon this basis.

Of the special clinical studies applicable to this situation particular interest attaches to the part ophthalmoscopy may play in the diagnosis of periarteritis nodosa in the future. From necropsy observations the occasional occurrence of scattered whitish foci of lymphocytic, monocytic and plasma cell infiltration in the choroid has been predicted (Goldstein and Wexler, 1929). Other ophthalmologists claim that the fundal changes noted in these patients are incidental to hypertension and renal insufficiency rather than peculiar to this disease. Electrocardiograms will reveal faults of conduction upon whatever basis they may arise, but in the present relation they serve as an important adjunct in assembling evidences of extensive and progressive vascular changes. The occasional development of coronary occlusion from this cause is of more than passing interest (Akesson, 1934). Further confirmation is required to establish the validity of the claim that the roentgenograms of the lung reveal characteristic changes in periarteritis nodosa (Herrmann, 1933).

The routine laboratory studies may lend important suggestive or supportive data toward the diagnosis. Upon urinalysis albumin, red blood cells and casts may appear in the active phase of the renal form of the disease. Advancing to the state of vascular occlusion the kidneys so involved may eliminate a urine of fixed low specific gravity; albumin, red blood cells and casts may then be less abundant in the urine. Pari passu with these urinary findings increasing renal insufficiency may evidence itself by the mounting levels of protein end-products in the blood. An inversion of the serum albumin-globulin ratio has been described (Middleton and McCarter, 1935). Phenolsulphonphthalein output may be progressively decreased under these conditions. Glycosuria may be expected in the instances of the disease with serious pancreatic involvement. Here also will appear deviations from normal sugar tolerance curves. The blood studies afford certain changes common to periarteritis nodosa. Anemia of the hypochromic microcytic order is the rule. Although it varies in intensity, this anemia may assume extreme degrees. Leucocytosis has been reported in approximately a third of the cases (Curtis and Coffey, 1934); but this would appear to be an underestimation of its frequency. Furthermore, eosinophilia appeared in 12 per cent of the cases reviewed by the same workers. From personal experience and a review of the pathologic sequence of the periarteritic lesions it seems fair to assume that an overwhelming majority of these patients would possibly show an eosinophilia at some time in their course, if they were followed by routine blood studies consecutively from the beginning to the end of the disease. In degree this eosinophilia may be extreme (79 per cent, Strong, 1928), a circumstance which may itself be directional.

Finally the biopsy of the periarteritic nodules promises to have an increasingly important place in diagnosis. The first intra vitam diagnosis by Kussmaul and Maier (1866) was confirmed by the study of the affected arteries in excised muscle. Hence, upon suspicion, where the characteristic periarteritic nodules are not available for section, recourse to the biopsy of voluntary muscle is advised. Negative findings in either or both of these directions should not exclude the diagnosis, since the lesions are notoriously uneven in their distribution. The chance diagnosis of this condition has followed the histologic demonstration of the classical lesions in materials obtained upon exploratory laparotomy, cholecystectomy, appendectomy, herniorrhaphy, nephrectomy, vasectomy and amputation of a leg.

The differential diagnosis of periarteritis nodosa is difficult and involved. Von Haun (1920) lists "trichinosis, Werlhof's disease, typhoid fever, miliary tuberculosis, polymyositis, arteriosclerosis with sclerosis of the kidneys, neuritis multiplex, gastroenteritis, pyemia, hemorrhagic nephritis, serositis tuberculosa, influenza with renal hemorrhage, purpura hemorrhagica" as erroneous diagnoses in this condition, nor does this list exhaust the possibilities of confusion. As indicated, the tetrad of Meyer (1921) and Brinkmann (1922) offers the logical direction of clinical attack; but beyond a question of doubt most cases of periarteritis nodosa escape intra vitam recognition by reason of a lack of awareness of its varied and bizarre manifestations. Given the picture of obscure sepsis, vague abdominal symptoms, polymyositis, polyneuritis, wasting, renal insufficiency, hypochromic microcytic anemia and eosinophilia, in detail or fragmentarily, the diagnosis of periarteritis nodosa should be entertained. Not infrequently the visceral manifestations arouse a diagnostic consciousness of this possibility by reason of the dispersion of symptoms and signs indicating a widespread vascular lesion in a patient whose dominant features have previously suggested a septic background. The clinching evidence of the biopsy should be sought in accessible subcutaneous nodules or, if not available, in the voluntary muscle. Even in the absence of this conclusive evidence the diagnosis of periarteritis nodosa may be clearly derived from the clinical picture with or without other laboratory support.

The prognosis of periarteritis nodosa is always grave; but it is entirely probable that many patients survive attacks with or without serious permanent handicap. Up to the present time certain students of the subject have viewed this position with skepticism; but clinical and pathologic evidence is accumulating in its support. There would seem to be no reasonable objection to the assumption of an ability to survive such attacks as are marked by a limited extent of invasion and by a relative escape of vital organs in the process. Indeed Horton, Brown and Magath (1935) have clearly demonstrated the occurrence of a non-fatal form of periarteritis nodosa limited to the temporal arteries. Surviving episodes of varying severity, cases reported by Spiro (1919), as clinically latent and pathologically obsolete, may be predicted. In instances terminating fatally Curtis and Coffey (1934) give a duration ranging from 6 days to 6 years. Recent reviews favor Grüber's average of 4.7 years (1926).

While isolated examples of remissions apparently incident to therapy have been reported, no true specific is recognized and treatment is still directed toward the symptomatic indications. If there be a history of syphilis or if the Wassermann reaction be positive, the arsenicals are advised; but in the absence of this possible etiology its trial has usually been unavailing. In last analysis the rational treatment of periarteritis nodosa must await the elucidation of its etiology and pathogenesis.

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